REMARKS

The Claim Amendments

Claims 1-12, 14-23, 37, 39-53, 61 and 62 are pending in this application. Claims 13 and 63-69 are canceled in this response. Claims 24-36, 38 and 54-60 were previously canceled. Applicant reserves the right to file for and obtain claims directed to the subject matter of the canceled claims in continuing and divisional applications claiming priority and benefit from the present application.

Applicant has amended claims 1 and 48 to improve their form and more particularly to point out and distinctly claim the subject matter which applicant regards as his invention. In particular, applicant has amended claims 1 and 48 to recite the determination of at least one coefficient comprising a complex number by parallel computational means. Support for this amendment is found throughout the application as originally filed at, for example, pg. 17, line 21 to pg. 19, line 4; and pg. 23, lines 1-22.

Applicant has also amended claims 1 and 48 to delete the phrase "any one of the set of presumed values 0° and 90°" in step (g) and to substitute therefor the phrase "phase angle values of 0° or 90°." Support for this

amendment is found throughout the application as originally filed at, for example, pg. 23, lines 8-11.

Applicant has further amended claims 1 and 48 to delete the term "becomes" in step (e) and to substitute therefor the phrase "can be converted into." Support for this amendment is found throughout the specification as originally filed at, for example, pg. 32, lines 1-17.

Applicant has amended claims 1, 7, 39, 40, and 48 to delete the term "complex-valued" and to substitute therefor the phrase "which comprises a complex number" or "complex-number." Support for this amendment is found throughout the specification as originally filed at, for example, pg. 11, lines 4-5.

Applicant has amended claim 2 to delete the phrase "improvements by" in response to the Examiner's objection.

Finally, applicant has amended claim 9 to delete the phrase "to allow iterative improvement of the electron density of the model" in response to the Examiner's objection.

These amendments add no new matter. They also are clarifying in nature and do not change the scope of the original claims.

THE REJECTIONS

35 U.S.C. § 112, second paragraph

Claims 1-12, 14-23, 37, 39-53, 61 and 62 stand rejected under 35 U.S.C. 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter that applicant regards as his invention.

(1) Claim 1 and 48, step (g)

The Examiner contends that claims 1 and 48, as previously amended to recite a "method of using parallel computational means", are vague and indefinite. In the Examiner's view, neither claim recites active steps for performing parallel computational means when practicing the claimed method.

Applicant has amended claims 1 and 48 to clarify step (g). The amendment clarifies that in step (g) the determination of the at least one coefficient comprising a complex number is done by parallel computational means. This amendment to claims 1 and 48 (and claims 2-12, 14-23, 37, 39-47, 49-53, 61 and 62 which depend therefrom) obviates the Examiner's rejection.

The Examiner has also objected to the term "the set of presumed values" recited in step (g), lines 2-9 of claims 1 and 48. The Examiner contends that the term has insufficient antecedent basis.

Applicant has amended claims 1 and 48 to delete the phrase "the set of presumed values", thereby obviating the Examiner's objection.

(2) Claim 1 and 48, step (e)

The Examiner has objected to the term "becomes" in step (e), line 3 of claims 1 and 48, stating that the term causes the claims to be vague and indefinite. In the Examiner's view, it is unclear how each spherical harmonic spherical Bessel (SHSB) function "becomes" a Fourier representation.

Applicant has amended claims 1 and 48 at step (e) to delete the term "becomes" and to substitute therefor the phrase "can be converted into." Applicant submits that amended claims 1 and 48 clarify that an individual SHSB basis function, centered at a specific position, can be mathematically converted into a Fourier representation of a basis function that has been positionally translated. The amendments to claims 1 and 48 (and claims 2-12, 14-23, 37,

39-47, 49-53, 61 and 62 which depend therefrom) obviate the Examiner's rejection.

(3) Claims 1 and 48, step(g)

The Examiner has also objected to step (g) of claims 1 and 48 as vague and indefinite. The Examiner states that it is unclear how the calculation of the Fourier representation of each SHSB basis function is accomplished in step (g) when such step has been achieved in step (f).

Applicant has amended claims 1 and 48 such that step (e) (which was step (f) prior to the November 12, 2003 amendment) recites modifying at least one SHSB basis function so that it can be converted into a Fourier representation of a positionally translated basis function. Step (f) (which was step (g) prior to the November 12, 2003 amendment) then recites the step of calculating the Fourier representation. This amendment eliminates any redundancy and obviates the Examiner's objection.

(4) Claims 1, 39, 40 and 48, steps (g) and (h)

The Examiner has objected to the term "complex-valued" as recited in claim 1, steps (g) and (h); claim 39, line 5; claim 40, line 4; and claim 48, step (g) as being

vague and indefinite. The Examiner states that "it is unclear what criteria is being used to consider that a coefficient is 'complex-valued'".

Applicant has amended claims 1, 39, 40, and 48 to clarify them by deleting the term "complex-valued" and substituting therefor the phrase "which comprises a complex number." The amended claims now clarify the original scope, i.e., that the coefficient constitutes a complex number, which is, as defined by the Merriam-Webster's Collegiate Dictionary, Tenth Edition, "a number of the form $a + b\sqrt{-1}$ where *a* and *b* are real numbers". The amendments to claims 1, 39, 40 and 48 obviate the Examiner's rejection.

(5) Claims 2 and 9

The Examiner has objected to the term "improvements" as recited in claim 2, line 5; and claim 9, line 3 as being vague and indefinite. The Examiner states that it is unclear what is being improved (the process of modeling or the data generated from the process).

Applicant has amended claim 2 to delete the phrase "improvements by" and has amended claim 9 to delete the phrase "to allow iterative improvement of the electron

density of the model." These amendments obviate the Examiner's rejection.

In view of the above arguments and amendments, applicant requests that the Examiner withdraw his rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, first paragraph

(1) Written Description

Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61 and 62 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner argues that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor had possession of the claimed invention at the time the application was filed.

In particular, the Examiner asserts that the limitation "scale factors and correlation coefficients of the phase angle...are calculated at any one of the set of presumed values 0° and 90°" in claims 1 and 48, step (g), is new matter. The Examiner acknowledges that applicant discloses that only two alpha angles need be calculated to determine Fsolo, having an alpha phase angle of either 0 or

90 degrees. The Examiner states, however, that while the instant specification specifies that it is only necessary to calculate two presumed values of α, 0° and 90°, this is different from the limitation "calculated at any one of the set of presumed values 0° and 90°."

Applicant has amended claims 1 and 48 to delete the phrase "any one of the set of presumed values 0° and 90°" and substituted therefor "phase angle values of 0° or 90°." This amendment clarifies the claims but does not change its original scope. The claims always recited performing the calculation using phage angles 0° and 90°. As the Examiner has acknowledged, the specification, as originally filed, describes the calculation of scale factors and correlation coefficients using only the two phase angle values of 0° or 90°. Therefore, the amendments to claims 1 and 48 (and claims 3-8, 10-12, 14-23, 37, 39-47, 49-53, 61 and 62 which depend therefrom) obviate the Examiner's rejection, and applicant respectfully requests its withdrawal.

(2) Enablement

Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61 and 62 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly enabled only for determining the three-

dimensional structure of a *Staphylococcal aureus* nuclease, yet not being enabled for any other molecule.

The Examiner argues that the art of protein crystallization is an unpredictable art, citing Drenth, J. and New Focus, Science, 2002. The Examiner also contends that the instant claims are not applicable to all sets of pre-existing X-ray diffraction data sets. The Examiner then asserts that a method that relies on data from an unpredictable art, such as protein crystallization would require clear and precise guidance for one of skill in the art to reliably use the method. Hence, the Examiner concludes, in view of the difficulty of the protein crystallization process, it is unreasonable to expect one of skill in the art to use the information disclosed for one specific crystal for the application of the invention to any other crystal without having to exercise undue experimentation. Applicant traverses.

No undue experimentation would be required to apply applicant's claimed method to other crystals.

Applicant's disclosure teaches one of skill in the art means by which to mathematically generate three-dimensional representations of the electron density derived from x-ray diffraction data and to perform *ab initio* phasing. There are thousands of electron density maps in

the structural biological community. Each is available for use in, and can be solved with, applicant's claimed invention. Just as importantly, one of skill in the art would recognize that applicant's claimed invention can be applied to any electron density maps generated in the future, as well, without undue experimentation.

The Examiner's contention that crystallization is unpredictable does not change that fact. Applicant's invention is not about crystallization or the even earlier protein production or DNA cloning. It is about mathematically generating a three-dimensional structure from x-ray data. It is applicable to all x-ray data - that available today and that available tomorrow. It is a generic invention supported by many species.

The Examiner's position, if accepted, would mean that no generic invention that is applicable to future technology would be patentable. That is just not the case. The Cohen-Boyer patents for replicating DNA were based on a few examples but still applicable to today's newly cloned DNA. So to the Genentech early expression patents.

The application describes the application of the invention to one such electron density map. No undue experimentation is required to apply it to the many other maps now available in the art. The electron density maps

are all the data that are required to practice the claimed invention.

Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61 and 62 stand rejected under 35 U.S.C. 112, first paragraph, as enabled only for a method for determining the three-dimensional structure of a *Staphylococcal aureus* nuclease using equations 1-12 (pages 10-14), but not being enabled using any other mathematical equations. The Examiner contends that, in view of the difficulty of the protein crystallization process (*supra*) and in view of the supposed lack of guidance in the specification for using any other mathematical equations, it would be unreasonable to expect one of skill in the art to use the claimed invention without undue experimentation. Applicant traverses.

As explained *supra*, one of skill in the art of x-ray crystallography could routinely apply applicant's claimed invention to unphased electron density maps without undue experimentation. Given the guidance in the specification about how to use that data to determine the three-dimensional structure of a molecule, skilled artisans, undoubtedly familiar with the mathematics of x-ray diffraction analysis given the high level of skill in the art at the time the application was filed, would not require undue experimentation to alter applicant's specific

mathematical equations to their particular circumstances, or use the disclosed technique in conjunction with algorithms described in the prior art. Furthermore, given the mathematical nature of the instant invention, the level of predictability with regard to use of any altered set of applicant's equations would be high.

For all of these reasons, applicant requests that the Examiner reconsider and withdraw the current rejections under 35 U.S.C. § 112, first paragraph.

35 U.S.C. 102(b)

Claims 1-12, 14-23, 37, 39-53, 61 and 62 stand rejected as being anticipated by Friedman, J.M. Comput. Chem. Vol. 23, No. 1, pp. 9-23 (January 1999)(hereinafter "Friedman"). Applicant traverses.

The Examiner argues that, Friedman anticipates the claims because: 1) the limitation of parallel computational means is not given patentable weight in view of the 35 U.S.C. 112, first paragraph objection raised *supra*; and 2) the limitation bearing on the calculation of phase angles of the complex-valued coefficient is anticipated by Friedman at page 12, column 2, line 34 to page 13, line 18. Applicant traverses.

The text cited by the Examiner in Friedman neither describes nor anticipates the means by which one of skill in the art would calculate the phase of the complex number for each *lmn* index. On pg. 22, line 14 in the right-hand column, Friedman describes the calculation of the phase of the complex number as one "which optimizes the correlation coefficient between the Fourier representation of the basis function and the diffraction pattern." Therefore, Friedman does not teach one of skill in the art a direct calculation of the phases, but rather an optimization technique wherein multiple calculations would be required for each phase index. With the disclosure of Friedman in hand, one of skill in the art would have no reasonable expectation of success in determining the complex number phases with just two calculations as is done in applicant's invention. The Examiner points to no relevant disclosure in Friedman that teaches a method other than an optimization technique that requires multiple calculations.

In view of amended claims 1 and 48, applicant submits that the limitation of parallel computational means should be given patentable weight. Amended claims 1 and 48 now recite the use of parallel computational means in the body of the claim, at step (g), thereby obviating the

Examiner's objection to its placement solely within the preamble of the claim.

Friedman does not disclose applicant's novel parallelization scheme, an exemplary embodiment of which is taught in the instant application as more accurately and more rapidly determining α_{lmn} coefficients, resulting in the reduction of the time for the calculation to 18 hours when used in combination with applicant's calculation of two presumed angles for the spherical harmonic spherical Bessel coefficients for F_{solo} and F_{accum}. Friedman does not teach applicant's parallelization technique and, therefore, does not teach the skilled artisan how to achieve the results of applicant's invention with the same accuracy or the same speed that characterizes the methods of the pending claims

The Examiner contends that Friedman discloses a method for interconverting three-dimensional molecular spatial information with spherical harmonic-Bessel representation and non-centrosymmetric crystalline arrays, thereby anticipating claims 37 and 49. In view of the foregoing amendments and remarks, applicant traverses.

Friedman does not anticipate the methods of claims 37 and 49. One of skill in the art could not use the methodology of Friedman to determine α_{lmn} with the accuracy and speed of the present invention and therefore

could not describe a single asymmetric object in space by a three-dimensional SHSB expansion in the manner taught by applicant. Therefore, Friedman does not anticipate claim 37 or claim 49.

The Examiner also asserts that Friedman anticipates step (a) in claims 1 and 48 as well as claims 3, 16 and 50 by testing the method described therein with a few macromolecular crystals of known structure.

Friedman does not demonstrate parallel computation of α_{lmn} condensing determination of phase and amplitude into just two calculations. Therefore, application of Friedman's method to macromolecular crystals of known structure does not anticipate any of claims 1, 3, 16, 48 or 50.

The Examiner further asserts that claims 4 and 51 are anticipated by Friedman, insofar as that document discloses exhaustive searches to find the positional and rotational orientation of a known molecule in a new crystalline packing arrangement based upon a measured X-ray diffraction pattern with the Fourier phase information associated with said diffraction pattern unknown.

Friedman's exhaustive search schemes do not compute the scale factors and correlation coefficients for α_{lmn} in the same manner as the current invention nor do they

employ applicant's parallelization method. Therefore, the search methods of Friedman do not anticipate claim 4 or 51.

The Examiner further contends that step (b) in claims 1 and 48 and step (k) in claim 2 are anticipated by Friedman's disclosure that the method based upon orthogonal basis functions allows for two of the final three rotational degrees of freedom to be calculated by FFT and the final rotation calculated quickly by multiplying the spherical harmonic coefficients by a matrix as well as the disclosure of the use of DOCK for modeling the docking of ligands into a protein. The Examiner also contends that claims 1 and 48, in particular step (c), are anticipated by Friedman's disclosure of a resolution limit of 3.0 Å in the evaluation of the FFTs. And the Examiner asserts that claims 1 and 48, in particular steps (d) and (g), and claim 6 are anticipated by Friedman's disclosure of the selection of two arbitrary geometric parameters, radius and position, are determined for the unit cell lengths and angles in terms of the Fourier expansion. The Examiner further asserts that step (e) of claims 1 and 48 are anticipated by Friedman, insofar as that document discloses a prescreening step that reduces the number of translation points that need to be considered. The Examiner contends that step (f) of claims 1 and 48 is anticipated by Friedman's disclosure

of calculated interconversion between the spherical harmonic-Bessel representation and the Fourier representation. And the Examiner contends that claims 1 and 48, in particular steps (h), (i) and (j), as well as claims 7-9, 11 and 39-42 are anticipated by Friedman's disclosure that complex-valued coefficients, Fourier summations, and indices are calculated according to equations 3-5. The Examiner also contends that claim 2, in particular step (l), is anticipated by Friedman's recitation of a method designed to provide functional maxima or minima for each of the energy terms calculated. Applicants traverses.

As is well accepted, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Because Friedman does not disclose every element set forth in claims 1 and 48, it does not anticipate those claims. Nor can Friedman be made to do so via selection of individual elements of the claims and piecemeal comparison thereto. The teaching of Friedman must be regarded as a whole. Friedman does not disclose applicant's parallelization method, nor does it disclose

the computation of the amplitude and phase of α_{lmn} in a calculation sampling only two phase angles. Therefore, Friedman does not anticipate any of claims 1 or 48.

Claim 10 stands rejected as being anticipated by Friedman's disclosure that the value of zero is considered in the aforementioned calculations. Claim 5 stands rejected as being anticipated by Friedman's disclosure of a method for non-overlapping spherical expansion zones. Claim 12 stands rejected as being anticipated by Friedman's recitation of equations 6-8, which are used for converting from a series of spherical harmonic coefficients to one of Fourier structure factor amplitudes and phases.

Friedman does not anticipate each element of any of claims 5, 10 or 12, since Friedman does not teach applicant's parallelization scheme or its truncated phase angle search allowing for calculation of amplitude and phase in just two calculations.

Lastly, claims 14, 15, 17-23, 43-47, 52, 53, 61 and 62 stand rejected, in view of Friedman's recitation of the use of a DEC-alpha-4000 workstation for data input and output and model display.

Friedman does not anticipate each element of claims 14, 15, 17-23, 43-47, 52, 53, 61 or 62, since Friedman does not teach applicant's parallelization scheme

nor its truncated phase angle search allowing for calculation of amplitude and phase in just two calculations.

In view of these essential differences between applicant's methods and those of Friedman, Friedman does not anticipate the claims of the pending application. Accordingly, the claim rejections under 35 U.S.C. § 102(b) should be withdrawn.

CONCLUSION

Applicant respectfully requests that the Examiner consider the foregoing amendments and remarks, and pass the claims to issue.

Respectfully submitted,

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